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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,778	11/20/2000	Peter Muhlradt	29473/11899	9133

4743 7590 06/30/2003

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EXAMINER
AUDET, MAURY A

ART UNIT	PAPER NUMBER
1654	15

DATE MAILED: 06/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/716,778	MUHLRADT ET AL.	
	Examiner	Art Unit	
	Maury Audet	1654	

-- The MAILING DATE of this communication app ars on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,7,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

This application contains claims directed to the following patentably distinct species of the claimed invention:

I. A peptide sequence of claim 3; and

II. A compound of claim 10.

The four SEQ ID NOS: of claim 3 are each distinct peptides without a core structure, which may be conjugated to the compound of broad claim 1 at "Y". The compounds of claim 10 are each distinct compounds of broad claim 1, incorporating one of the sequences of claim 3.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1 and 7 are generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Nabeela McMillian, Attorney for Applicant, on 6/27/03, a provisional election was made of species (iv) of claim 10, SEQ ID NO: 8, corresponding to sequence species (iv), SEQ ID NO: 3, of claim 3, without traverse. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-19 are examined on the merits as drawn to the elected species.

Preliminary Amendment

Amendment of claims 1-19, from "use" claim language to "methods of use" is acknowledged. Amended claims 1-19 are examined on the merits.

Objections

The disclosure is objected to because of the following informalities:

Specification page 2, ¶ 2 recites "half-live", which appears to be grammatically incorrect. It is suggested that the phrase be amended to "half-life".

Claim 13 recites "and" instead of "are".

Appropriate correction is required.

Rejections

Claim Rejections - 35 USC § 112 1st ¶ Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a "written description" rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Vas-Cath Inc. V. Mahurka, 19 USPQ2d 1111, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the "written description" inquiry, is *whatever is now claimed*" (see page 1117).

The claimed invention is drawn to a method of treating a wound [i.e. infection] comprising administering a pharmaceutical composition comprising the general structure of claim 1, wherein "Y" is an amino acid of 1-25 residues (claim 1); any amino acid sequences that do not have an adverse influence on the water solubility of the lipopeptide or lipoprotein or any fragments or variants of the specific sequences (claim 3); or any lipopeptide or lipoprotein which carries at the N-terminal a dihydroxypropyl cysteine group with two, fatty acids bonded via ester bonds (claim 6); or any lipoprotein or lipopeptide obtained from any mycoplasma/*Mycoplasma fermentans* clone of claim 7 and 8.

One of skill in the art would not recognize from the disclosure that the Applicant was in possession of any compounds of general structure claim 1, with any amino acid of 1-25 residues, or of or fragments or variants of the specific sequences of claim 3. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (see *Vas-Cath* at page 1116). Namely, although the specification at page 5 describes 4 specific amino acid sequences, and at page 6 describe 5 compounds (2 of which use SEQ ID NO: 3 and differ only by their "R" configuration, or lack thereof) (see also claim 3, in part, and claim 10) and specification pages 7-20 describe the use of the specifically described compounds in treatment experiments; no other amino acid sequences or compounds with amino acid sequences have been described other than the above.

Thus, neither the claims nor the specification describes the amino acid sequences of 1 to 25, contemplated as the genus. With all the different combinations of amino acid residues that could be incorporated in sequence up to 25 amino acids in length, it is not clear what is contemplated for use in the present invention, other than the 4 amino acid sequences described. One of skill in the art would not recognize from the disclosure that the Applicant was in possession of the genus, namely all the amino acid combinations in sequences up to 25 amino acid residues in length, of which SEQ ID NO. 1-4 are merely species; any amino acid sequences that do not have an adverse influence on the water solubility of the lipopeptide or lipoprotein or any fragments or variants of the specific sequences (claim 3); or any lipopeptide or lipoprotein which carries at the N-terminal a dihydroxypropyl cysteine group with two, fatty acids bonded via ester bonds (claim 6); or any lipoprotein or lipopeptide obtained from any mycoplasma/ Mycoplasma fermentans clone (claim 7 and 8); for use in a method of treating an infection.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

35 U.S.C. §112, 1st ¶ Scope of Enablement

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the four specific sequences of claim 3 and the five specific compounds of claim 10 in a method of treating an infection, does not reasonably provide enablement for any peptide up to 25 amino acid residues in length claim 1; any amino acid sequences that do not have an adverse influence on the water solubility of the lipopeptide or lipoprotein or any fragments or variants of the specific sequences of claim 3; or any lipopeptide or lipoprotein which carries at the N-terminal a dihydroxypropyl cysteine group with two, fatty acids bonded via ester bonds of claim 6; or any lipoprotein or lipopeptide obtained from any mycoplasma/ *Mycoplasma fermentans* clone of claim 7 and 8; for use in a method of treating an infection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

> The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman,

230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The instant disclosure fails to meet the enablement requirement for a therapeutically effective pharmaceutical composition for the following reasons:

The nature of the invention: The claimed invention is drawn to a method of treating a wound [i.e. infection] comprising administering a pharmaceutical composition comprising the general structure of claim 1, wherein "Y" is an amino acid of 1-25 residues (claim 1); any amino acid sequences that do not have an adverse influence on the water solubility of the lipopeptide or lipoprotein or any fragments or variants of the specific sequences (claim 3); or any lipopeptide or lipoprotein which carries at the N-terminal a dihydroxypropyl cysteine group with two, fatty acids bonded via ester bonds (claim 6); or any lipoprotein or lipopeptide obtained from any mycoplasma/*Mycoplasma fermentans* clone (claim 7 and 8).

The state of the prior art and the predictability or lack thereof in the art:

The art teaches that the efficacy of therapeutics is dependent upon factors such as solubility of the drug, bioavailability at the target site, attainment of effective plasma concentrations, solubility in tissues, biotransformation, toxicity, proteolytic degradation, immunological inactivation, rate of excretion or clearance (half-life), deactivation by the liver, hydrolysis in serum, binding to plasma protein, and in the case of antivirals, propensity for emergence of resistant strains (see Benet et al., pp. 3-32, in The Pharmacological Basis of Therapeutics, 8th ed., 1990, page 3, first paragraph; page 5, second column, last partial paragraph, first two sentences; page 10, the paragraph bridging columns 1 and 2; page 18, the paragraph bridging columns 1 and 2; page 20, last full paragraph; and the paragraph bridging pages 20 and 21 and footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO BD> APP>& Inter. 1992).

Isolation, purification, formulation, and delivery of proteins represent significant challenges to pharmaceutical scientists, as proteins possess unique chemical and physical properties. These properties pose difficult stability problems (Abstract). With the recent advances in recombinant DNA technology, the commercial production of proteins for

> pharmaceutical purposes has become feasible. [] Unfortunately, proteins possess chemical and physical properties which present unique difficulties in the purification, separation, storage, and delivery of these materials. (Manning et al., Pharmaceutical Research, p. 903).
>
> Additionally, Mycoplasma and *Mycoplasma fermentans* are known causative factors in such infections as pneumonia; lacking cells walls and therefore resistant to many antibiotics (http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=mycoplasma&action=Search+OMD).

The amount of direction or guidance present and the presence or absence of working examples: Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The specification describes at page 5 describes 4 specific amino acid sequences, and at page 6 describe 5 compounds (2 of which use SEQ ID NO: 3 and differ only by their "R" configuration, or lack thereof) (see also claim 3, in part, and claim 10) and specification pages 7-20 describe the use of the specifically described compounds in treatment experiments.

The breadth of the claims and the quantity of experimentation needed: The claims are drawn broadly to a method of use, using not only any amino acid up to 25 residues, but essentially any lipopeptide/protein, which carries at the N-terminal a dihydroxypropyl cysteine group with two, fatty acids bonded via ester bonds (claim 6). Additionally, as noted, lipoprotein or lipopeptide obtained from any mycoplasma/*Mycoplasma fermentans* may be causative factors in such infections as pneumonia and potentially resistant to many antibiotics; if not isolated correctly. Absent sufficient teachings in the specification or art sufficient to overcome the teachings of unpredictability in the art as to enablement on whether the polypeptide can be "therapeutically effective" as a "pharmaceutical" composition; it would require undue

experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 112 2nd ¶

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is recites that the method's "lipoprotein is in the form of a solution . . . a plaster impregnated or coated with it". It is unclear what the term "it" means.

Assuming "it" is referring the "solution", it is suggested that "it" be deleted and "said solution" be inserted therein.

Claim 3 is drawn to "variants" of the four specific amino acid sequences of claim 3. The specification does not specifically describe any other peptide other than the four specific ones of claim 3. Therefore, it is unclear what is contemplated within the meaning of "variants", within claim 3.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-19 are rejected under 35 U.S.C. 102(a) as being anticipated by Muhlradt et al. (WO 98/27110).

WO 98/27110 teach the "S-[2,3-bispalmitoyloxypropyl}cysteinyl-GNNDESNISFKEK" compound isolated from a mycoplasma clone, specifically a Mycoplasma fermentans clone, which is water-soluble (abstract, page 3); as well as for an agent [i.e. for treatment] containing the afore-mentioned peptide [Applicant's elected species of claim 3 and 10, SEQ ID NOS: 3 and 8; and claims 1-12].

Claims 1-19 are rejected under 35 U.S.C. 102(a) as being anticipated by Muhlradt et al. (J. Exp. Med., June 2, 1997, pp. 1951-1958).

Muhlradt et al. teach the "S-[2,3-bispalmitoyloxypropyl}cysteinyl-GNNDESNISFKEK" compound isolated from a mycoplasma clone, specifically a Mycoplasma fermentans clone, which is water-soluble (abstract, introduction); having "highest specific MSA [macrophage stimulating activity] of so far described" (page 1952, ¶ 2); which may be useable in such solutions as vaccines, like other MSA compounds (page 1955, 2nd column, 1st ¶) [Applicant's elected species of claim 3 and 10, SEQ ID NOS: 3 and 8; and claims 1-12].

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Muhlradt et al. (J. Exp. Med., June 2, 1997, pp. 1951-1958) or Muhlradt et al. (WO 98/27110) in view of Fidler et al. (US 4916118).

Muhlradt et al. and WO 98/27110 are taught above. Both teach the use of S-[2,3-bispalmitoyloxypropyl}cysteinyl-GNNDESNISFKEK, but do not expressly teach the use of the compound in a solution for treatment of an infected tissue [Applicant's claims 11-12].

Fidler et al. teach the use of "2-palmitoyl derivatives . . . lipopetides having immunomodulating properties" (column 7, lines 33-35, 39-4) in pharmaceuticals as macrophage stimulators (column 8, lines 37-41).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the pharmaceutical agents incorporating 2-palmitoylthio derivatives and lipopeptides with the S-[2,3-bispalmitoyloxypropyl}cysteinyl-GNNDESNISFKEK compound of Muhlradt or WO 98/27110 because Fidler et al. teach that lipopeptides with 2-palmitoylthio derivatives, which the compound of Muhlradt and WO 98/27100 is a species of, in a pharmaceutical composition exhibit macrophage stimulating activity which beneficially produces an immune system response in the recipient [i.e. against infection].

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maury Audet whose telephone number is 703-305-5039. The examiner can normally be reached from 7:00 AM – 5:30 PM, off Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at 703-306-3220. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-1234 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

MA
June 22, 2003

LEONB. LANKFORD, JR.
PRIMARY EXAMINER

6/27/3